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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,535	10/30/2003	David T. Curiel	678503-2001.1	7880

7590 07/13/2009

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EXAMINER	
EPPS -SMITH, JANET L	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
07/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,535	CURIEL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6-30-08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27-32,34-44 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *43 and 44* is/are allowed.

6)☒ Claim(s) *25,27-32,34-42 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-14-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-14-09 has been entered.

2. Claims 25, 27-32, 34-44, and 47 are presently pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

4. Claims 25-27, 30-32, 34, and 39-42 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. (Mol. Ther. 7(5, Part 2): S420, abstract 1089), May 2003, in view of Curiel et al., WO 00/67576, and Adachi et al. (see IDS)

5. Takayama discloses treatment of lung cancer with a CRAd comprising an E1 region under control of the human VEGF promoter and modification of its fiber by replacement of the knob with that ofAd3. Curiel is illustrative of the state of the CRAd art at the time Takayama was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of cancer.

6. In addition, Takayama teaches an embodiment wherein a HSV tk gene is co-administered with the CRAd in a "non-replicative" adenoviral vector, which produces a

synergistic anti-cancer effect. Takayama does not teach to modify the fiber by insertion of an RGD-containing peptide into the HI loop or to include the HSV tk gene in the CRAd. Moreover, Takayama et al. also does not teach a deletion of nucleotides 324 to 488 of the E1A promoter region from the Ad5 genome, which is replaced by insertion of the tumor-specific promoter.

7. Curiel teaches that as an alternative to replacing the knob portion of the fiber with that of a different adenovirus, one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). Curiel also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously, intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

8. Adachi et al. teach the design of conditionally replicative Ads, which show tumor specific replication and oncolysis, see the following vectors, wherein in one embodiment a tumor specific promoter sequence is inserted into nucleotides 324-488 of the E1 promoter, see Figure 1:

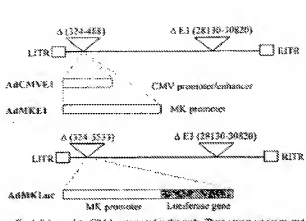

Fig. 1. Scheme of the CRAd vectors used in this study. These vectors are constructed from E3 region-deleted Ad5 backbone and do not contain the Ad E1A promoter region expanding from nucleotide 324 to 458 of the Ad genome. Deletion of the E3 region was necessary, because the MK promoter we chose was too long to insert into the Ad genome without deletion of introduced E3 region. AdCMVE1 and AdMKE1 differ in the promoter driving E1A expression. Only AdMKLuc is the carcinoembryonic Ad control. We also use Ad-wt as a control.

9. The AdMKE1 CRAd has expression specificity for tumor cells which are MK-positive, the MK promoter controls the expression of E1. This strategy was used for the CRAd specific expression in neuroblastoma and Ewing's sarcoma.

10. Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Takayama by insertion of an RGD peptide into the HI loop, rather than be replacement of the fiber knob, since Curiel taught that this modification was a suitable alternative for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, rather than on a separate vector, since Curiel taught that such a modification of a CRAd was useful for treating cancer, and including the tk gene in the CRAd would eliminate the necessity of preparing two separate adenovirus and improve the frequency of co-transfection of a tumor cell by both CRAd and HSV tk gene to provide an additional means to kill tumor cells. Additionally, it would have been obvious to have designed a modified CRAd by

introducing the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488, since Adachi et al. clearly describe modified CRAd comprising the insertion of a tumor specific promoter into this region of the E1 promoter, wherein the tumor specific promoter was able to drive tumor specific expression of the E1 gene. Absent evidence of unexpected results insertion of the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488 is clearly a matter of design choice, one of ordinary skill in the art would have had a reasonable expectation of success in producing a functional CRAd comprising the insertion of a tumor specific promoter into nucleotides 324-488 of the E1 promoter since Adachi et al. provides specific guidance in this regard.

11. Claims 25, 27, 30-32, 34 and 39-42 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576 and Adachi et al.

12. Curiel (2002) generally describes CRAd for use in treatment of cancer comprising a fiber modified by insertion of ligands into the HI loop or by replacement with the knob of an adenovirus of another serotype, wherein the E1 region of the CRAd is placed under control of a tumor specific promoter, such as the VEGF promoter, and the CRAd may contain a heterologous therapeutic gene, encoding a heat shock protein that increases increase potency of the CRAd. WO 00/67576 is illustrative of the state of the CRAd art at the time Curiel was published, and shows that at this time one of skill in this art was aware of how to prepare CRAds and administer them in treatment of

cancer. Although Curiel (2002) does not explicitly disclose how the CRAd is administered, the administration routes listed claim 14 cover nearly all methods of administering CRAd.

13. Curiel (2002) has been described above. Curiel does not teach to modify the fiber by insertion of an RGD-containing peptide, specifically, into the HI loop, to include the HSV tk gene in the CRAd. Moreover, Curiel does not teach to insert the tumor specific promoter into nucleotides 324-488 of the E1 promoter region.

14. However, WO 00/67576 teaches that one can overcome the reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22). WO 00/67576 also teaches to include a therapeutic gene, such a gene encoding HSV tk, in the CRAd to provide an additional means of killing tumor cells in a patient. Gancyclovir is administered following administration of the CRAd. To effect treatment of cancerous tumors, CRAds are administered intravenously, intraperitoneally, systemically, orally or intratumorally. See for example, pages 23-24.

15. Adachi et al. teach the design of conditionally replicative Ads, which show tumor specific replication and oncolysis, see the following vectors, wherein in one embodiment a tumor specific promoter sequence is inserted into nucleotides 324-488 of the E1 promoter, see Figure 1 (set forth above). The AdMKE1 CRAd has expression specificity for tumor cells which are MK-positive, the MK promoter controls the expression of E1. This strategy was used for the CRAd specific expression in neuroblastoma and Ewing's sarcoma.

16. Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Curiel by insertion of an RGD peptide into the HI loop, since WO 00/67576 taught that this modification was effective for improving infectivity of a tumor cell by a CRAd and one knew how to make such a modification. It also would have been obvious to have included the HSV tk gene in the CRAd, since WO 00/67576 taught that such a modification of a CRAd was useful for treating cancer to provide an additional means to kill tumor cells. As indicated in the instant specification, the VEGF promoter is not efficient at directing transcription in normal liver cells, consequently limitation recited in claim 39 is an inherent characteristic of a CRAd whose replication is dependent upon the VEGF promoter. Additionally, it would have been obvious to have designed a modified CRAd by introducing the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488, since Adachi et al. clearly describe modified CRAd comprising the insertion of a tumor specific promoter into this region of the E1 promoter, wherein the tumor specific promoter was able to drive tumor specific expression of the E1 gene. Absent evidence of unexpected results insertion of the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488 is clearly a matter of design choice, one of ordinary skill in the art would have had a reasonable expectation of success in producing a functional CRAd comprising the insertion of a tumor specific promoter into nucleotides 324-488 of the E1 promoter since Adachi et al. provides specific guidance in this regard.

17. Claims 25, 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 in view of Curiel et al., WO 00/67576 and Adachi et al.

18. Molnar-Kimber teaches CRAds and methods of using the CRAds for the treatment of cancer (e.g. pages 8-12, claims 1-32). The CRAds comprise an E1A gene under control of a tumor specific promoter, such as the survivin promoter (e.g. page 11, ¶ 1; claims 5 and 18) to render the CRAd conditionally-replicative in tumor cells. The CRAd may also contain a therapeutic gene encoding HSV tk to augment the oncolytic activity, where gancyclovir is also administered (e.g. page 16, lines 7-12; page 30, lines 3-16). For treating cancer, the CRAd is administered intravenously, intraperitoneally, systemically, orally or intratumorally (page 31, lines 13-24). Molnar-Kimber does not teach to modify the adenoviral fiber either by insertion of an RGD peptide into the HI loop or by replacing the knob with that of a different adenovirus. Furthermore, Molnar-Kimber does not teach wherein the tumor specific promoter is inserted into nucleotides 324-488 of the E1 promoter.

19. However, Curiel teaches that the loss of CAR in tumor cells reduces the infectivity by adenovirus, thereby reducing the effectiveness of treating cancer with CRAds having a wild-type fiber (page 19). Curiel teaches that this reduced infectivity of tumor cells by adenovirus due to loss of CAR in the tumor cell can be overcome by genetically altering the fiber gene of the CRAd so that a CDCRGDCFC oligopeptide is inserted into the HI loop (e.g. pages 21-22) or the knob is replaced by that of an adenovirus that binds to receptors other than CAR, e.g. of Ad3.

20. Adachi et al. teach the design of conditionally replicative Ads, which show tumor specific replication and oncolysis, see the following vectors, wherein in one embodiment a tumor specific promoter sequence is inserted into nucleotides 324-488 of the E1 promoter, see Figure 1 (set forth above). The AdMKE1 CRAd has expression specificity for tumor cells which are MK-positive, the MK promoter controls the expression of E1. This strategy was used for the CRAd specific expression in neuroblastoma and Ewing's sarcoma.

21. Therefore, it would have been obvious at the time the invention was made to have modified the fiber of the CRAd of Molnar-Kimber by insertion of an RGD peptide into the HI loop or by replacement of the fiber knob with that of a different adenovirus, since Curiel taught that loss of CAR by tumor cells reduced the infectivity of CRAds (based on Ad 5) and that these modifications of the fiber were effective for improving infectivity of a tumor cell by a CRAd, and one knew how to make such a modification. Additionally, it would have been obvious to have designed a modified CRAd by introducing the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488, since Adachi et al. clearly describe modified CRAd comprising the insertion of a tumor specific promoter into this region of the E1 promoter, wherein the tumor specific promoter was able to drive tumor specific expression of the E1 gene. Absent evidence of unexpected results insertion of the tumor specific promoter into the E1 promoter region corresponding to nucleotides 324-488 is clearly a matter of design choice, one of ordinary skill in the art would have had a reasonable expectation of success in producing a functional CRAd comprising the insertion of a tumor specific

promoter into nucleotides 324-488 of the E1 promoter since Adachi et al. provides specific guidance in this regard.

22. Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003, in view of Curiel et al., WO 00/67576, and Adachi et al. as applied to claims 25, 26, 28, 29, 34, 35 and 39 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002.

23. Claims 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, abstract 3287, March 2002) in view of Curiel et al., WO 00/67576 and Adachi et al., as applied to claims 25, 27, 30-32, 34 and 39-42 above, and further in view of Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002.

24. Takayama et al. (2003), in view of Curiel et al. and Adachi et al., has been described above, and does not teach that the method can be used to treat ovarian, gastric, and pancreatic cancers. The combination of Curiel in view of Curiel et al. and Adachi et al. has been described above for teaching a CRAd with an Ad5/Ad3 chimeric fiber and VEGF promoter, and does not teach that the method can be used to treat lung cancer, such as non-small cell lung carcinoma, and ovarian, gastric, and pancreatic cancers.

25. However, Takayama et al. (2002) teaches that neovascularization is crucial for tumor growth and metastasis, that VEGF is well known as a key factor in tumor-

associated angiogenesis, and that many different kinds of tumor exhibit increased expression of VEGF. Takayama (2002) discloses that AdVEGFE1, which is a hAd5-based CRAd having a VEGF promoter operably linked to the E1A region, is effective for killing lung, ovarian, gastric and pancreatic cancer cells, and Ad5/Ad3 VEGFE1, which is the same as AdVEGFE1 except that the fiber proteins are chimeric with a hAd3 knob domain, was even more effective in killing lung cancer cells. Takayama teaches that the mechanism of tumor-associated angiogenesis is common to many different types of cancer and that AdVEGFE1 may have universal application for treating cancer.

26. Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have used the method of cancer treatment with an hAd5 vector having a VEGF promoter controlling its replication by operable linkage to the E1 region and a chimeric fiber protein with the knob domain of Ad3 of Takayama et al. (2003) in view of Curiel and Adachi et al. or of Curiel in view of Curiel et al. and Adachi et al., to treat lung, ovarian, gastric and pancreatic cancer with a reasonable expectation of success, since Takayama (2002) taught that a CRAd having a VEGF promoter controlling replication was effective for killing these types of cancer and others, and that inclusion of the Ad3 knob domain made the CRAd even more effective for lung cancer, and since the tumor-associated angiogenesis mechanism is common to various types of cancer, one would expect the inclusion of the Ad3 knob on the fiber protein would make it more effective on tumors of other types of cancer as well.

Double Patenting

27. Claims 25, 27-32, 34-42, and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 9-12 of U.S. Patent No. 6,824,771 in view of Curiel et al., WO 00/67576; Takayama et al. Mol. Ther. 7(5, Part 2): S420, abstract 1089, May 2003; Takayama et al., Mol. Ther. 5(5, Part 2): S268, abstract 821, May 2002, and Adachi et al.

28. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims embrace an obvious variant of the subject matter claimed in the '771 patent. The instant claimed invention differs from the invention of the patent primarily in the modification that renders the adenovirus conditionally-replicative. The patented invention involves mutations in E1 genes (CRAd type I), whereas the CRAd of the instant invention involves placing one or more adenoviral early genes under control of a tumor-specific promoter (CRAd type II). However, WO 00/67576 at pages 19-20, for example, discloses that type I and type II CRAds are suitable alternatives for treating cancer, and the replication selectivity of a CRAd, such as a CRAd type I or CRAd type II with only E1 genes being controlled by a tumor-specific promoter, can be improved by placing additional early genes under control of tumor-specific promoters, such as the PSA, CEA or SLPI promoters. Curiel et al. also describes including herpes tK genes in the CRAd and treating with gancyclovir. Takayama (2003) also discloses CRAds that have a chimeric fiber, and have early genes under control of a VEGF promoter, to achieve efficient replication in tumors cells, but not normal cells, and Takayama (2002) discloses that a CRAd whose replication is

directed by a VEGF promoter is effective at killing a variety of different tumor cells, such as lung, ovarian, gastric and pancreatic tumor cells, because it targets a common mechanism of tumor-associated angiogenesis. Also the issued claims do not teach to insert the tumor specific promoter into a deletion in the E1 promoter region of nucleotides 324-488. However, the prior art provides explicit guidance in creating a modified CRAd by insertion of a tumor specific promoter into a deletion of 324-488 of the E1 promoter region, wherein tumor specific expression of the E1 genes is produced, see Adachi et al.

29. Consequently, it would have been obvious to one of skill in the art at the time the instant invention was made to have placed early genes under control of tumor specific promoters, by insertion of the promoter into nucleotides 324-488 as instantly claimed, rather than relying upon mutations in E1 genes, as in the patented invention, to limit replication to tumors, because Curiel et al. taught that both means of promoting replication of the CRAd in tumor cells, but not in normal cells, were suitable alternatives, and that placing additional early genes under control of tumor-specific promoters further restricts viral replication to tumors and reduces its replication in normal cells, see Adachi et al.

Response to Arguments

Claim Rejections - 35 USC § 112

30. The rejection of claims 25, 27-32, 34-42, and 47 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn.

31. The rejection of claims 25, 27-32, 34-42, and 47 under 35 U.S.C. 112, second paragraph, is withdrawn in response to Applicant's amendment.

Conclusion

32. Claims 43-44 are allowable over the prior art.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

34. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

35. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633